RESEARCH REVIEW

Pain Management in the Ehlers–Danlos Syndromes

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Chronic pain in the Ehlers–Danlos syndromes (EDS) is common and may be severe. According to one study, nearly 90% of patients report some form of chronic pain. Pain, which is often one of the first symptoms to occur, may be widespread or localized to one region such as an arm or a leg. Studies on treatment modalities are few and insufficient to guide management. The following is a discussion of the evidence regarding the underlying mechanisms of pain in EDS. The causes of pain in this condition are multifactorial and include joint subluxations and dislocations, previous surgery, muscle weakness, proprioceptive disorders, and vertebral instability. Affected persons may also present with generalized body pain, fatigue, headaches, gastrointestinal pain, temporomandibular joint pain, dysmenorrhea, and vulvodynia. Pain management strategies may be focused around treating the cause of the pain (e.g., dislocation of a joint, proprioceptive disorder) and minimizing the sensation of pain. Management strategies for chronic pain in EDS includes physical therapy, medications, as well as durable medical equipment such as cushions, compressive garments, and braces. The different modalities are discussed in this paper. © 2017 Wiley Periodicals, Inc.

KEY WORDS: Ehlers–Danlos syndrome; hypermobility; pain; proprioception; neuropathic; joint pain; pelvic pain

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INTRODUCTION

Pain is common in Ehlers–Danlos syndrome (EDS) and may correlate with hypermobility, frequency of subluxations and dislocations, soft tissue injury, history of previous surgery, myalgias, and may become chronic [Sacheti et al., 1997; Mulvey et al., 2013]. Pain may be musculoskeletal or widespread. It may be acute and/or chronic. The pain may interfere with socialization and activities of daily living. It can often affect sleep quality (which is common in EDS), which in turn contributes to functional impairment, independent of the level of fatigue [Voermans et al., 2009].

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Overall, pain impacts health-related quality of life.

Pain is common in Ehlers–Danlos syndrome (EDS) and may correlate with hypermobility, frequency of subluxations and dislocations, soft tissue injury, history of previous surgery, myalgias, and may become chronic. Pain may be musculoskeletal or widespread.

Multiple pathologies likely contribute to pain in EDS since it is a disease of connective tissue, which is found in virtually every organ system (Table I). The following is a literature review and discussion of the evidence of the underlying mechanisms contributing to pain in this complex disorder with management considerations.

METHODS

An international group of physicians with experience in treating pain in EDS formed a working group under the auspices of the International Consortium on the Ehlers–Danlos Syndromes. The working group conferenced by telephone approximately twice a month starting mid-2015. The working group then met in Paris, France, and again in New York in 2016 to hone the description, management, and future directions.

A detailed literature search was done on PubMed with the following keywords: "Hypermobility," "Ehlers–Danlos Syndrome," connective tissue, collagen, and pain. Papers selected were case series, case controlled studies and reviews. Case reports were not formally included but were scanned for any additional information.

LITERATURE REVIEW

Sacheti et al. [1997] interviewed 51 patients with EDS of which 28 (55%) were diagnosed with EDS hypermobile type (hEDS). They reported that the incidence of pain in hEDS was 28 out of 28 (100%). In this population, the mean score on the Numerical Rating Scale was 8 out of 10 for all types of EDS. Out of the 28 patients with hEDS, 24 (85.7%) reported progressively worsening pain. The authors concluded that moderate to severe pain is common in hEDS, starts early in life and progresses and evolves over time but that it is often complex and varied, frequently reporting pain at multiple locations.

In a more recent study of 273 patients with EDS by Voermans et al. [2009], 246 (90%) patients reported pain. Of the 246 patients who reported pain, 230 (93%) of them reported joint hypermobility, 193 (78%) had a history of dislocations, 236 (96%) reported dermal features, 227 (92%) had previous surgery, and muscle weakness was reported by 196 (80%). The hEDS was diagnosed in the majority (59%), of which, 95% were females.

Pain is often initially more localized to joints or limbs initially. Musculoskeletal pain in EDS is influenced by external factors such as lifestyle, sport activities, trauma, surgery, and various co-morbidities. Many patients report their very first painful sensations acutely, in relation to joint traumas such as dislocations and sprains as well as "growing pains" mostly localized to the knees/thighs [Castori et al., 2013]. Approximately 30% of children with hEDS reported arthralgias, back pain, and myalgias. This rate increases to >80% in patients over 40 years of age [Castori et al., 2011]. It is inversely correlated to generalized joint hypermobility, as assessed by the Beighton score, as those over the age of 33 years, often have a "negative" Beighton score but yet pain symptomatology in all aspects continues and, in most cases, increases.

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Children are often not believed by practitioners about their pain much less their joint hypermobility [Gazit et al., 2016]. While it may be acute and musculoskeletal, many also present with more recurring or chronic pain [Cattalini et al., 2015; Stern et al., 2016]. Such chronic pain issues, especially abdominal pain, are often misdiagnosed as a behavioral condition or Munchausen by proxy in children and young adults [Fikree et al., 2016]. Children may also present with recurrent, unexplained bruising or multiple joint subluxations and dislocations whereby parents are accused of child abuse [Castori, 2015].

One study found that pain was most frequently localized in the neck, shoulders, hips, forearms, and legs in 40 EDS patients [Voermans et al., 2009]. Neck pain is a common feature of hEDS and is frequently associated with headaches. It is often difficult to segregate the two conditions. Loose ligaments in the cranio-cervical junction and cervical spine may manifest as occipital-atlanto and/or atlanto-axial instability [Menezes and Van Gilder, 1988; Menezes et al., 2001]. This is compounded by ligamentous laxity of the cervical spine [Da Silva et al., 1992; Henderson et al., 2005a] and may present as cervical-medullary syndrome, with other presenting symptoms including difficulty swallowing, speech difficulty,

TABLE I. Review of Literature of Types of Pain in hEDS

Manifestations	Number of patients studied	Incidence (%)	References
Generalized body pain	>800 (cumulative)	90	Jerosch and Prymka [1996]; Camerota et al. [2011]; Hamonet et al. [2012, 2014]; Hamonet and Brock [2015]; Scheper et al. [2015]; Voermans and Knoop, 2011
Soft-tissue pain	>800 (cumulative)	90	Hudson et al. [1998]; Hamonet et al. [2012, 2014]; Scheper et al. [2015]
Dislocations	>800 (cumulative)	78	Voermans et al. [2010]; Hamonet et al. [2012, 2014]
Joint pain	28* 232# 644^	Elbow (43)* Shoulders (80)* Hands (75)* Knees (71)* Spine (67)*	Moore et al. [1985]; Aktas et al. [1989]*; Sacheti et al. [1997]; Tubiana [2000]; Berglund et al. [2005]; McCulloch and Redmond [2010]; Hamonet et al. [2012]^; Hamonet et al. [2014]; Hamonet and Brock, 2015#]; Christopherson and Adams [2014]; Scheper et al. [2015]
Fatigue	644 [cumulative] 11 [cumulative]	95 6 (55)*	Gulbahar et al. [2006]; Voermans et al. [2009, 2010]; *Celletti et al. [2012]; Hamonet et al. [2012]
Bone loss	23	16 (70)	Gulbahar et al. [2006]
Neuropathic pain	29*	68*	DeGraaf [1973]; Kass and Kayed [1979]; Stoler and Oaklander [2006]*; Camerota et al. [2011]; Voermans et al. [2011]
Loss of proprioception	18*, 32#, 22^	Significant *P*-value	Helliwell [1994]*; Ferrell et al. [2004]; Fatoye et al. [2009]; #Rombaut et al. [2010]; Zarate et al. [2010]; Celletti et al. [2011]; Galli et al. [2011]; ^Clayton et al. [2013]; Smith et al. [2013]; Deparcy [2016]
Headaches	28*	75*	Sansur et al. [2003]; Schievink et al. [2004]; DeCoster et al. [2005]; Henderson et al. [2005a]; Gulbahar et al. [2006]; Milhorat et al. [2007]*; Bendik et al. [2011]; Rozen [2014]; Hamonet and Brock [2015]
Gastrointestinal pain	21*	85.7*	Douglas and Douglas [1973]; Petros and Swash [2008]; Castori et al. [2010]*; Zarate et al. [2010]; Dordoni et al. [2015]; Hamonet and Brock [2015]; Mohammed et al., 2010
Temporomandibular joint pain	42*	71.4*	*DeCoster et al. [2004, 2005]; Hagberg et al. [2004]
Menorrhagia	387	77.57	Gompel [2016]
Dysmenorrhea		73.1	
Vulvodynia/ dyspareunia	387	42	Gompel [2016]

dysautonomia, gait changes, weakness, spasticity, and sensory alteration [Henderson et al., 2005b; Hamonet et al., 2012]. See also "Neurological and Spinal Features of Ehlers-Danlos Syndrome," this issue [Henderson et al., 2017].

Bendik et al. [2011] reported multiple headache types among 28 hEDS female patients in an interview-style case-control study. Headaches, in particular migraine, was higher in prevalence and more often more disabling than the control population (N = 232). Castori et al. [2015] reported the incidence of headaches in no less than 1/3 of patients with EDS with migraines as the most common headaches. Other possible causes of headaches include tension-type headache, new daily persistent headache, temporomandibular joint dysfunction (TMD), Chiari malformation, cervicogenic, neck–tongue syndrome, and medication related [Neilson and Martin, 2014].

Other major cause of headaches in EDS patients includes TMD [Milhorat et al., 1999]. TMD may be present in more than 70% of patients with EDS [DeCoster et al., 2004, 2005]. See also "Oral and Mandibular Manifestations in the Ehlers-Danlos Syndromes," this issue [Mitakides and Tinkle, 2017]. Cervicogenic and new daily persistent headache have also been reported to be associated with cervical spine hypermobility in a small series of EDS patients [Rozen, 2014]. Tension-type is very common as well predominantly among those with neck and shoulder dysfunction and pain.

Many joints have involvement in EDS. Patients with hEDS present commonly with pain in their hands and wrists, especially those with repetitive use [Quarrier, 2011]. They report increased pain to the forearm from the constant muscle strain. The thumb basilar joint is a particularly common joint involved in hEDS because it relies, in large part, on ligaments for stability [Christophersen and Adams, 2014]. A

study of 55 patients with EDS showed a highly significant correlation between the presence of electrophysiologically proven carpal tunnel syndrome and the occurrence of hEDS [Aktas et al., 2008]. As is often seen in many other musculoskeletal chronic pain conditions, the pain is most often at the insertion site. See also "Role of Orthopedic Management in the Ehlers-Danlos Syndromes," this issue [Ericson and Wolman, 2017].

CHRONIC PAIN

Chronic pain is one of the major symptoms presented by patients with hEDS [Sacheti et al., 1997; Voermans et al., 2010]. It often presents as diffuse body pain affecting almost every part of the body. It is common and may be severe [Voermans et al., 2009]. In one study, the prevalence of chronic pain was 90% in patients with various types of EDS, with the highest scores on severity of pain found in hEDS [Voermans et al., 2009].

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Loss of proprioception in hEDS has been reported in the medical literature and is considered to be an important factor in hEDS-related chronic pain [Helliwell, 1994; Ferrell et al., 2004; Fatoye et al., 2009; Clayton et al., 2013; Smith et al., 2013]. Proprioception, also known as joint position sense, is the ability of a joint to determine its position, detect movement, and sense of resistance to force [Rombaut et al., 2010]. Proprioception is essential for maintaining the balance of the human body, detecting movement, and coordination of normal activities. It helps protect the joints from hyperextending and damaging ligaments [Stillman, 2002].

Several different hypotheses have been brought forward to explain poor proprioception in hEDS [Smith et al., 2013]. Two such hypotheses are that the excessive joint mobility may damage proprioceptive receptors in the joints [Fatoye et al., 2009] or that the sensation of pain in the joint may diminish proprioception [Felson et al., 2009]. Exercises to enhance proprioception demonstrated an improvement in pain [Ferrell et al., 2004]. Improvement of proprioception may be effective for ameliorating both the functional status, including balance, and chronic pain [Clayton et al., 2013]. Chronic pain is associated with motor and proprioceptive disturbances; it is not clear if this is due to disturbances in position sense, muscle spindle function, or central representations of the body [Tsay et al., 2015].

Often, hEDS may be misdiagnosed as fibromyalgia because of diffuse pain with a strong myofascial component. These are to be considered as two distinct conditions with very specific diagnostic criteria. They may co-exist as two separate conditions but have different etiologies. The 2010 classification of fibromyalgia which has a sensitivity of 88% only has many overlapping features with EDS [Wolfe et al., 2010].

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The evidence to show the precise mechanisms of pain in hEDS is weak. Many of the proposed mechanisms have been drawn from other chronic pain conditions. Studies to distinguish both pathologies are very necessary. Pain and fatigue have a high prevalence in EDS, frequently manifesting as the predominant symptoms and as the most disabling features [Rombaut et al., 2011]. Clinical examination, pain questionnaires, quantitative sensory testing, and neurophysiological responses disclosed no somatosensory nervous system damage. Conversely, quantitative sensory testing, documented hyperalgesia to cold and heat stimuli, and an increased wind up ratio implied central sensitization [Rombaut et al., 2015; Scheper et al., 2016]. This suggests that the pain related to EDS probably shares mechanisms with those underlying fibromyalgia [Di Stefano et al., 2016]. In a study of 206 female patients with EDS, the impact of pain and functional impairment was similar to fibromyalgia but worse than that of rheumatoid arthritis [Rombaut et al., 2011].

Any form of pain be it nociceptive or neuropathic may be a secondary or even tertiary effect of underlying causes. It is those underlying causes that need to be treated. Pain management should be as diverse as its presentation and treated from all angles [Ferrell et al., 2004; Gulbahar et al., 2006; Felson et al., 2009; Voermans et al., 2009; Camerota et al., 2011; Galli et al., 2011; Castori et al., 2012; Hamonet et al., 2012; Gompel, 2016; Scheper et al., 2015; Deparcy, 2016; Hugon-Rodin et al., 2016].

MANAGEMENT

Management of chronic pain in hEDS is hindered by lack of evidence based studies that clearly demonstrate effectiveness of different modalities. The way to manage pain in hEDS would be to adapt and alter options that are used in the non-EDS population. Chronic pain

is a symptom but is also a disease entity by itself with demonstrated changes in the nervous system. Chronic pain maybe nociceptive (pain resulting from tissue injury), or neuropathic (pain generated ectopically and abnormally by either the peripheral or central nervous system) [Pappagallo, 2005; Pappagallo and Werner, 2008]. Most cases of chronic pain are an uneven mix of nociceptive and neuropathic pain. Pain management strategies may be focused around treating the cause of the pain (e.g., dislocation of a joint) and minimizing the sensation of pain.

1. Successful management of chronic pain requires a multidisciplinary approach.
2. Physiotherapy: available evidence suggests that patients who receive exercise intervention improve over time [Palmera et al., 2014]. Physical rehabilitation consists of core stabilizing and joint stabilizing and proprioception enhancing exercise coupled with general fitness program [Grahame, 2009; Rozen, 2014]. Stretching exercises should be limited to gentle stretching to avoid any risks of subluxations or dislocations. Techniques that have been used in treating hEDS pain include manual therapy for overactive muscles, trunk stabilization, posture re-education, joint awareness using biofeedback, joint mobilization with muscle release [Simmonds and Keer, 2008]. See also "The evidence-based rational for physical therapy treatment of children, adolescents and adults diagnosed with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobile type," this issue [Engelbert et al., 2017].
3. Cognitive behavioral therapy: this approach is applicable to all patients especially those whose pain is intractable, life dominating and unresponsive to analgesics or other physical interventions [Grahame, 2009]. To date there have been no clinical trials to demonstrate its efficacy in EDS.
4. Pharmacological choices:

(a) Non-steroidal anti-inflammatory drugs (NSAIDs): May be helpful if the pain is of inflammatory origin. Chronic use of NSAIDs is frequently associated with gastrointestinal, renal, and hematologic consequences [Sacheti et al., 1997]. They may also worsen symptoms of MCAS (mast cell activation syndrome) which may be a co-morbidity in hEDS. See also "Mast Cell Disorders in the Ehlers-Danlos Syndromes," this issue [Seneviratne et al., 2017].

(b) Opioids: for acute, severe pain, opioids may be an option, but only for a short duration. There is good evidence that long-term treatment with opiates is not a viable option and may lead to central pain sensitization. A trial of tramadol may be a valuable alternative for some patients with hEDS [Sunshine et al., 1992; Brown and Stinson, 2004]. The specific risk of using opioids in hEDS is centered on worsening gastrointestinal issues such as constipation and nausea as well as increasing symptoms of MCAS.

(c) Options for neuropathic pain include low dose tricyclic anti-depressants, anti-convulsants, and selective norepinephrine reuptake inhibitors. They have been shown to be effective to treat neuropathic pain in non-EDS patients; however, no trials have been done in hEDS to show their efficacy. There is concern in hEDS that if given to treat pain they might worsen other symptoms such as dysautonomia.

(d) Acetaminophen, to avoid hematologic consequences that could be associated with NSAIDs.

(e) Topical lidocaine for localized pain after subluxations as well as painful gingival tissue [Hamonet and Brock, 2015].

(f) Nefopam is a non-morphine derived potent analgesic [Hamonet and Brock, 2015].

(g) For musculocutaneous pain: injections with 1% lidocaine into trigger points [Hamonet et al., 2014; Hamonet and Brock, 2015].

(h) For dyspareunia: lubricants and/or topical estrogens (twice a week) combined with hyaluronic acid and benzydamine. In the most severe cases, lidocaine gel just before intercourse [Gompel, 2016; Hugon-Rodin et al., 2016].

(i) Dysmenorrhea can be treated with NSAIDs as it is often time-limited [Gompel, 2016; Hugon-Rodin et al., 2016].

(j) Women with dysmenorrhea and whose overall symptoms worsen during the peri-menstrual period may be aided by hormonal control with anti-gonadotropic, hypoestrogenic progestins [Gompel, 2016; Hugon-Rodin et al., 2016]. This might be due to the fact that proprioceptive accuracy decreases during menses [Fouladi et al., 2012].

(k) Transcutaneous neuro stimulator (TENS) to block pain signals via gate control theory [Hamonet and Brock, 2015].

(l) Anti-decubitus cushions and mattresses can be used for pain and discomfort when sitting/working and to improve sleep [Hamonet and Brock, 2015].

(m) Treating the underlying proprioceptive disorder with compressive, that is, tight clothing, physiotherapy, and proprioceptive shoe inserts [Hamonet et al., 2010; Hamonet and Brock, 2015].

(n) Dystonia has been described in 54% of EDS patients in a cohort study of 626 patients. Treatment with Levodopa/carbidopa or Levodopa 50 mg/benserazide 12.5 may improve dystonia, pain, and fatigue [Hamonet et al., 2016a].

(o) Fatigue and pain are linked when it comes to disability issues. They both diminish the quality of life and need to be addressed. Treating the fatigue treats the pain and vice versa. Dysautonomia is a common factor in EDS and when treated may alleviate both fatigue and pain [Bravo, 2010].

FUTURE DIRECTIONS

The management of the often severe, changing, debilitating pain in patients with hEDS is currently insufficient. Traditional pain medications do not seem to adequately treat most patients probably because the underlying cause is different to most other pain. It is, therefore, our understanding that studies not only into pain management itself are

necessary to decrease the pain but also into the management of fatigue, dystonia, energy consumption, and the treatment of the impaired proprioception among others.

It is our opinion that studies into the following subjects are urgently needed:

- Studies to differentiate between fibromyalgia and hEDS are needed as the cause of pain in hEDS may be different to that of fibromyalgia and require different treatment. Many patients are being (mis)diagnosed with fibromyalgia and thus not treated for all the other symptomatology and co-morbidities that might occur with hEDS.
- Earlier diagnosis might lead to better preventive measures. Prospective studies that look at the outcome of proprioceptive treatment on pain, fatigue, and other symptoms are necessary to evaluate if early intervention can decrease symptom progression. It is thus necessary to study tools for diagnosing EDS in children [Deparcy, 2016].
- Research on the use of NSAIDs including the differentiation between acute and chronic use in conjunction with the increased hemorrhagic tendency in hEDS.
- Oxygen therapy by face mask is already approved for cluster migraines. Oxygen therapy by face mask has been shown to decrease pain in EDS [Hamonet and Brock, 2015; Hamonet et al., 2016b]. Studies on oxygen therapy in the use against migraines and fatigue in hEDS are warranted.
- Studies into the treatment of proprioceptive impairment and its reduction of the different aspects of pain and fatigue.
- Gompel [2016] suggest that a systematic prospective study is needed to confirm the hypothesis on the role of hormonal modulation in pain management in this population.
- Studies on the treatment of dystonia, which seems to increase the occurrence of subluxations and thus pain, are necessary.
- Dysfunctions reported with oxidative phosphorylation, electron transport chain activity, and ATP production and recycling cause alterations in energy metabolism contributing to fatigue [Filler et al., 2014]. Studies considering a possible link of pain and fatigue in hEDS due to mitochondrial dysfunction are thus warranted.
- Low Dose Naltrexone (LDN) may be a good option for patients with neuropathic pain, mixed nociceptive and neuropathic pain, and pain secondary to autoimmune dysfunction in patients with hEDS. Naltrexone suppresses activation of microglia thus attenuating the production of proinflammatory cytokines. This effect is achieved by using very low doses of naltrexone [Chopra and Cooper, 2012]. Anecdotal reports of LDN in the management of chronic pain in hEDS have been promising.

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REFERENCES

Aktas JG, Mochizuki C, Rinsky LA. 1989. Trapeziometacarpal abnormalities in Ehlers-Danlos syndrome. J Hand Surg Am 14:89–94.

Aktas I, Ofluoglu D, Albay T. 2008. The relationship between benign joint hypermobility syndrome and carpal tunnel syndrome. Clin Rheumatol 27:1283–1287.

Bendik EM, Tinkle BT, Al-shuik E, Levin L, Martin A, Thaler R, Atzinger CL, Rueger J, Martin VT. 2011. Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. Cephalalgia 31:603–613.

Berglund B, Nordstrom G, Hagberg C, Mattiasson AC. 2005. Foot pain and disability and disability in individuals with Ehlers-Danlos syndrome (EDS): Impact on daily life activities. Disabil Rehabil 27:164–169.

Bravo JF. 2010. Ehlers-Danlos syndrome (EDS), with special emphasis in the joint hypermobile syndrome. Revista Medica de Chile 137:1488–1497.

Brown SC, Stinson J. 2004. Treatment of pediatric chronic pain with tramadol hydrochloride: Siblings with Ehlers-Danlos syndrome-hypermobility type. Pain Res Manag 9:209–211.

Camerota F, Celletti C, Castori M, Grammatico P, Padua L. 2011. Neuropathic pain is a common feature in Ehlers-Danlos syndrome. J Pain Symptom Manage 41: e2–e4.

Castori M, Camerota F, Celletti C, Danese C, Santilli V, Saraceni VM, Grammatico P. 2010. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: A pilot study on 21 patients. Am J Med Genet Part A 152A:556–564.

Castori M, Sperduti I, Celletti C, Camerota F, Grammatico P. 2011. Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type). Clin Exp Rheumatol 29:998–1005.

Castori M, Morlino S, Celletti C, Celli M, Morrone A, Colombi M, Camerota F, Grammatico P. 2012. Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type): Principles and proposal for a multidisciplinary approach. Am J Med Genet Part A 158A:2055–2070.

Castori M, Morlino S, Celletti C, Ghibellini G, Bruschini M, Grammatico P, Blundo C, Camerota F. 2013. Re-writing the natural history of pain and related symptoms in the joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. Am J Med Genet Part A 161A:2989–3004.

Castori M. 2015. Ehlers-Danlos syndrome(s) mimicking child abuse: Is there an impact on clinical practice? Am J Med Genet C Semin Med Genet 169:289–292.

Castori M, Morlino S, Ghibellini G, Celletti C, Camerota C, Grammatico P. 2015. Connective tissue, Ehlers-Danlos syndrome(s), and head and cervical pain. Am J Med Genet Part C 169C:84–96.

Cattalini M, Khubchandani R, Cimaz R. 2015. When flexibility is not necessarily a virture: A review of hypermobility syndromes and chronic or recurrent musculoskeletal pain in children. Pediatr Rheumatol Online J 13:40.

Celletti C, Castori M, Galli M, Rigoldi C, Grammatico P, Albertini G, Camerota F. 2011. Evaluation of balance and improvement of proprioception by repetitive muscle vibration in a 15-year-old girl with joint hypermobility syndrome. Arthritis Care Res 63:775–779.

Celletti C, Galli M, Cimolin V, Castori M, Albertini G, Camerota F. 2012. Relationship between fatigue and gait abnormality in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. Res Dev Disabil 33:1914–1918.

Chopra P, Cooper MS. 2012. Treatment of complex regional pain syndrome (CRPS) using low dose naltrexone (LDN). J Neuroimmune Pharmacol 8:470–476.

Christophersen C, Adams JE. 2014. Hand syndromes. Ehlers-Danlos syndrome. J Hand Surg Am 39:2542–2544.

Clayton HA, Cressman EK, Henriques DY. 2013. Proprioceptive sensitivity in Ehlers-Danlos syndrome patients. Exp Brain Res 230: 311–321.

Da Silva JA, Brito JC, da Nsbrega PV. 1992. Autonomic nervous system disorders in 230 cases of basilar impression and Arnold-Chiari deformity. Neurochirurgia (Stuttg) 35:183–188.

DeCoster PJ, Martens LC, Van den Berghe L. 2004. Prevalence of temporomandibular joint dysfunction in Ehlers-Danlos syndromes. Orthodontics Craniofacial Res 7:237–241.

DeCoster PJ, Van den Berghe L, Martens LC. 2005. Generalized joint hypermobility and temporomandibular disorders: Inherited connective tissue disease as a model with maximum expression. J Orofac Pain 19:47–57.

DeGraaf AS. 1973. Neuralgic amyotrophy in identical twins with Ehlers-Danlos syndrome. Eur Neurol 9:190–196.

Deparcy D. 2016. Propriocpetion et posture dans le syndrome d'Ehlers-Danlos. J de Readaptaton Medicale 36:38–42.

Di Stefano G, Celletti C, Baron R, Castori M, Di Franco M, La Cesa S, Leone C, Pepe A, Cruccu G, Truini A, Camerota F. 2016. Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. Eur J Pain 20:1319–1325.

Dordoni C, Ritelli M, Venturini M, Chiarelli N, Pezzani L, Vascellaro A, Calzavara-Pinton P, Colombi M. 2015. Recurring and generalized visceroptosis in Ehlers-Danlos syndrome hypermobility type. Am J Med Genet Part A 161A:1143–1147.

Douglas BS, Douglas HM. 1973. Rectal prolapse in the Ehlers–Danlos syndrome. Austr Paediatr J 9:109–110.

Engelbert RH, Juul-Kristensen B, Pacey V, de Wandele I, Smeenk S, Woinarosky N, Sabo S, Scheper MC, Russek L, Simmonds JV. 2017. The evidence-based rationale for physical therapy treatment of children, adolescents and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers-Danlos syndrome. Am J Med Genet Part C.

Ericson WB Jr., Wolman R. 2017. Role of orthopedic management in Ehlers-Danlos syndrome. Am J Med Genet Part C.

Fatoye F, Palmer S, Macmillan F, Rowe P, van der Linden M. 2009. Proprioception and muscle torque deficits in children with hypermobility syndrome. Rheumatology (Oxford) 48:152–157.

Felson DT, Gross KD, Nevitt MC, Yang M, Lane NE, Torner JC, Lewis CE, Hurley MV. 2009. The effects of impaired joint position sense on the development and progression of pain and structural damage in knee osteoarthritis. Arthritis Rheum 61:1070–1076.

Ferrell WR, Tennant N, Sturrock RD, Ashton L, Creed G, Brydson G, Rafferty D. 2004. Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum 50:3323–3328.

Fikree A, Aktar R, Morris JK, Grahame R, Knowles CH, Aziz Q. 2016. The association between Ehlers-Danlos syndrome-hypermobility type and gastrointestinal symptoms in university students: A cross-sectional study. Neurogastroenterol Motil. doi: 10.1111/nmo.12942. [Epub ahead of print].

Filler K, Debra L, James B, Nancy M, Ronald E, Lukkahatai N, Saligan LN. 2014. Association of mitochondrial dysfunction and fatigue: A review of the literature. BBA Clin 1:12–24.

Fouladi R, Rajabi R, Naseri N, Pourkazemi F, Geranmayeh M. 2012. Menstrual cycle and knee joint position sense in healthy female athletes. Knee Surg Sports Traumatol Arthrosc 20:1647–1652.

Galli M, Rigoldi C, Celletti C, Mainardi L, Tenore N, Albertini G, Camerota F. 2011. Postural analysis in time and frequency domains in patients with Ehlers-Danlos syndrome. Res Dev Disabil 32:322–325.

Gazit Y, Jacob G, Grahame R. 2016. Ehlers-Danlos syndrome-hypermobility type: A much neglected multisystem disorder. Rambam Maimonides Med J 7:e0034.

Gompel A. 2016. Les manifestations gynecologiques du syndrome d'Ehlers-Danlos hypermobile. Journal de Readaptaton Medicale 36:64–66.

Grahame R. 2009. Joint hypermobility syndrome pain. Curr Pain Headache Rep 13:427–433.

Gulbahar S, Şahin E, Baydar M, Bircan C, Kızıl R, Manisalı M, Akalın E, Peker O. 2006. Hypermobility syndrome increases the risk for low bone mass. Clin Rheumatol 25:511–514.

Hagberg C, Berglund B, Korpe L, Anderson-Norinder J. 2004. Ehlers-Danlos syndrome (EDS) focusing on oral symptoms: A questionnaire study. Othod Craniofac Res 7:178–185.

Hamonet C, Laouar R, Vienne M, Brissot R, Bernard JC. 2010. Comberg A. Vêtements compressifs et syndrome d'Ehlers-Danlos. Étude multicentrique et prospective sur 49 personnes du handicap avec le Handitest. Journal de Réadaptation Médicale 30: 184–191.

Hamonet C, Ravaud P, Villeneuve S, Gompel A, Serre N, Fredy D, Deparcy D, Mazaltarine G, Zeitoun JD, Metlaine A, Léger D, Benachi A, Cordier AG, Césaro P, Loche C, Dantchev N, Vienne M, Séjourné C, Laouar N, Gogly B, Landru MM, Moussa Badran S, Raffray Y, Challe G, Doursounian L, Mohler J. 2012. Ehlers-Danlos syndrome (about 664 cases). Statistical analysis of clinical signs from 644 patients with a Beighton scale≥4/9. Abstracts book of First International Symposium on the Ehlers-Danlos syndrome, Ghent, Belgium, p. 114.

Hamonet C, Gompel A, Raffray Y, Zeitoun JD, Delarue M, Vlamynck E, Haidar R, Mazaltarine G. 2014. Multiple pains in Ehlers-Danlos syndrome. Description and proposal of a therapy protocol. Douleurs 15:264–277.

Hamonet C, Brock I. 2015. Joint mobility and Ehlers-Danlos syndrome (EDS). New data based on 232 cases. J Arthritis 4:148.

Hamonet C, Ducret L, Marié-Tanay C, Brock I. 2016a. Dystonia in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type). SOJ Neurol 3:1–3.

Hamonet C, Vienne M, Leroux C, Letinaud MP, Paumier J, Dehecq B, Metlaine A, Brock I, Bird FM. 2016b. Manifestations respiratoires dans le syndrome d'Ehlers-Danlos (SED) Nouveaux apports therapeutiques. Journal de readaptaton medicale pratique et formation en medicine physique et de readaptation 36:56–61.

Helliwell PS. 1994. Impaired proprioceptive acuity at the proximal interphalangeal joint in patients with the hypermobility syndrome. Br J Rheumatol 33:1192–1193.

Henderson FC, Benzel EC, Kim D, Vaccaro AR. 2005a. Pathophysiology of cervical myelopathy: Biomechanical concepts. In: Benzel EC, editor. Spine Surgery: Techniques, complication avoidance, and management, 2nd edition, Vol 2. Philadelphia: Elsevier Churchill Livingstone. pp 100–108.

Henderson FC, Geddes JF, Vaccaro AR, Woodard E, Berry KJ, Benzel EC. 2005b. Stretch-associated injury in cervical spondylotic myelopathy: New concept and review. Neurosurgery 56:1101–1113.

Henderson F, Austin C, Banzel E, Bolognese P, Ellenbogen R, Francomano C, Ireton C, Klinge P, Koby M, Long D, Patel S, Singman E. 2017. Neurological and spinal manifestations of the Ehlers-Danlos syndromes. Am J Med Genet Part C.

Hugon-Rodin J, Lebègue G, Becourt S, Hamonet C, Gompel A. 2016. Gynecologic symptoms and the influence on reproductive life in 386 women with hypermobility type Ehlers-Danlos syndrome: A cohort study. Orphanet J Rare Dis 11:124.

Hudson N, Fitzcharles MA, Cohen M, Starr MR, Esdaile JM. 1998. The association of soft-tissue rheumatism and hypermobility. Br J Rheumatol 37:382–386.

Jerosch J, Prymka M. 1996. Proprioception and joint stability. Knee Surg Sports Traumatol Arthrosc 4:171–179.

Kass B, Kayed K. 1979. Acute multiple brachial neuropathy and Ehlers-Danlos syndrome. Neurology 29:1620–1621.

McCulloch R, Redmond A. 2010. The hypermobile foot. In: Hakin A, Keer R, Grahame R, editors. Hypermobility, fibromyalgia and chronic pain. London: Elsevier Churchill Livingstone.

Menezes A, Ryken T, Brockmeyer D. 2001. Abnormalities of the craniocervical junction. In: McLone DG, editor. Pediatric neurosurgery. Surgery of the developing nervous system, 4th edition. Philadelphia: WB Saunders. pp 400–422.

Menezes AH, Van Gilder JC. 1988. Transoral-transpharyngeal approach to the anterior craniocervical junction. Ten-year experience with 72 patients. J Neurosurg 69:895–903.

Milhorat TH, Chou MW, Trinidad EM, Kula RW, Mandell M, Wolpert C, Speer MC. 1999. Chiari I malformation redefined: Clinical and radiographic findings for 364 symptomatic patients. Neurosurg 44:1005–1017.

Milhorat TH, Bolognese PA, Nishikawa M, McDonnell NB, Francomano CA. 2007. Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation type I in patients with hereditary disorders of connective tissue. J Neurosurg Spine 7:601–609.

Mitakides J, Tinkle B. 2017. Oral and mandibular manifestations in the Ehlers-Danlos syndromes. Am J Med Genet Part C.

Mohammed SD, Lunniss PJ, Zarate N, Farmer AD, Grahame R, Aziz Q, Scott SM. 2010. Joint hypermobility and rectal evacuatory dysfunction: An etiological link in abnormal connective tissue? Neurogastroenterol Motil 22:1085–e283.

Moore JR, Tolo VT, Weiland AJ. 1985. Painful subluxation of the carpometacarpophalangeal joint of the thumb in Ehlers Danlos syndrome. J Hand Surg Am 10:661–663.

Mulvey MR, Macfarlane GJ, Beasley M, Symmons DP, Lovell K, Keeley P, Woby S, McBeth J. 2013. Modest association of joint hypermobility with disabling and limiting musculoskeletal pain: Results for a large-scale general population-based survey. Arthritis Care Res 65:1325–1333.

Neilson D, Martin VT. 2014. Joint hypermobility and headache: Understanding the glue that

binds the two together-part 1. Cephalalgia 54:1393–1402.
Palmera S, Bailey S, Barker L, Barney L, Elliott A. 2014. The effectiveness of therapeutic exercise for joint hypermobility syndrome: A systematic review. Physiotherapy 100:220–227.
Pappagallo M, editor. 2005. The neurological basis of pain. New York: McGraw-Hill.
Pappagallo M, Werner M. 2008. Chronic pain—A primer for physicians. London: Remedica.
Petros P, Swash M. 2008. A musculo-elastic theory of anorectal function and dysfunction in the female. Pelviperineology 27:86–122.
Quarrier F. 2011. Is hypermobility syndrome (HMS) a contributing factor for chronic unspecific wrist pain in a musician? If so, how is it evaluated and managed? Work 40:325–333.
Rombaut L, De Paepe A, Malfait F, Cools A, Calders P. 2010. Joint position sense and vibratory perception sense in patients with Ehlers-Danlos syndrome type III (hypermobility type). Clin Rheumatol 29:289–295.
Rombaut L, Malfait F, De Paepe A, Rimbaut S, Verbruggen G, De Wandele I, Calders P. 2011. Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: A comparative study with fibromyalgia and rheumatoid arthritis. Arthritis Rheum 63:1979–1987.
Rombaut L, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert R, Calders P. 2015. Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: Evidence for generalized hyperalgesia. Clin Rheumatol 34:1121–1129.
Rozen TD. 2014. New daily persistent headache: An update. Curr Pain Headache Res 18:431.
Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P. 1997. Chronic pain is a manifestation of the Ehlers-Danlos syndrome. J Pain Symptom Manage 14:88–93.
Sansur CA, Heiss JD, DeVroom HL, Eskioglu E, Ennis R, Oldfield EH. 2003. Pathophysiology of headache associated with cough in patients with Chiari I malformation. J Neurosurg 8:453–458.
Scheper MC, de Vries JE, Verbunt J, Engelbert RH. 2015. Chronic pain in hypermobility syndrome and Ehlers-Danlos syndrome (hypermobility type): It is a challenge. J Pain Res 8:591–601.
Scheper MC, Pacey V, Romabut L, Adams RD, Tofts L, Claders P, Nicholson LL, Engelbert RH. 2016. Generalized hyperalgesia in children and adults diagnosed with hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type: A discriminative analysis. Arthritis Care Res. doi: 10.1002/acr.22998. [Epub ahead of print].
Schievink WI, Gordon OK, Tourje J. 2004. Connective tissue disorders with spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: A prospective study. Neurosurgery 54:65–70.
Seneviratne SL, Maitland A, Afrin L. 2017. Mast cell disorders in Ehlers-Danlos syndrome. Am J Med Genet Part C.
Simmonds JV, Keer RJ. 2008. Hypermobility and the hypermobility syndrome, Part 2: Assessment and management of hypermobility syndrome: Illustrated via case studies. Man Ther 13:e1–e11.
Smith TO, Jerman E, Easton V, Bacon H, Armon K, Poland F, Macgregor AJ. 2013. Do people with benign joint hypermobility syndrome (BJHS) have reduced joint proprioception? A systematic review and meta-analysis. Rheumatol Int 33:2709–2716.
Stern CM, Pepin MJ, Stoler JM, Kramer DE, Spencer SA, Stein CJ. 2016. Musculoskeletal conditions in a pediatric population with Ehlers-Danlos syndrome. J Pediatr. pii: S0022-3476(16)31212-4. doi: 10.1016/j.jpeds.2016.10.078
Stillman BC. 2002. Making sense of proprioception. The meaning of proprioception, kinaesthesia and related terms. Physiother 88:667–676.
Stoler JM, Oaklander AL. 2006. Patients with ehlers danlos syndrome and CRPS: A possible association? Pain 123:204–209.
Sunshine A, Olson NZ, Zighclhoim I, DeCastro A, Minn FL. 1992. Analgesic oral efficacy of tramadol hydrochloride in post-operative pain. Clin Pharmacol Ther 51:740–746.
Tsay A, Allen TJ, Proske U, Giummarra M. 2015. Sensing the body in chronic pain: A review of psychophysical studies implicating altered body representation. Neurosci Biobehav Rev 52:221–232.
Tubiana R. 2000. Anatomy of the hand and upper limbs. In: Tubiana R, Amadio PC, editors. Medical problems of the instrumentalist musician, 1st edition. London: Martin Dunitz. pp 5–53.
Voermans NC, van Alfen N, Pillen S, Lammens M, Schalkwijk J, Zwarts MJ, van Rooij IA, Hamel BCJ, van Engelen BG. 2009. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Ann Neurol 65:687–697.
Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. 2010. Pain in Ehlers Danlos syndrome is common, severe and associated with functional impairment. J Pain Symptom Manage 40:370–378.
Voermans NC, Knoop H, van Engelen BG. 2011. High frequency of neuropathic pain in Ehlers-Danlos syndrome: An association with axonal polyneuropathy and compression neuropathy? J Pain Symptom Manage 41:e4–e6.
Voermans NC, Knoop H. 2011. Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 33:706–707.
Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DJ, Katz RS, Mease P, Russell A, Russell IJ, Winfield J, Yunus M. 2010. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 62:600–610.
Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, Aziz Q. 2010. Unexplained gastrointestinal symptoms and joint hypermobility: Is connective tissue the missing link? Neurogastroenterol Motil 22:252–278.